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(54) Title: A DEVICE FOR THE DELIVERY OF A DRUG TO A FRACTURED BONE

(57) Abstract: The present invention relates to a bone fixation device, such as a screw or fixation pin or wire, said device including a body containing or being coated with a drug selected from bisphosphonates. The device may be used in a number of procedures to promote healing of a bone, including promoting union of a fracture, to provide internal fixation due to osteoporosis, and in the treatment of osteonecrosis or osteochondritis dissecans.



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A Device for the Delivery of a Drug to a Fractured Bone

Field of the Invention

- 5 The present invention relates to a drug for use in bone healing. More specifically, the present invention relates to the use of bisphosphonates to increase the amount of healing bone around a fracture when delivered to the region of a fracture by a fixation device.

10 Background of the Invention

- While most commonly used for the prevention of bone resorption, bisphosphonates have recently been noted to promote bone growth and fracture repair. Research has shown that intravenous bisphosphonates
15 increase the rate of bone formation in distraction osteogenesis. Administration of oral bisphosphonates may also be effective.

- While intravenous and oral administration of the drug may be effective, it may also be useful in certain circumstances to provide a local or regional dose of bisphosphonate at and around the fracture site rather than administering the
20 drug systemically.

 The present invention aims to provide a delivery system for bisphosphonates which enables a therapeutically effective amount of a bisphosphonate to be delivered to a desired regional site of bone.

25 Summary of the Invention

 In a first aspect, the present invention consists in a bone fixation device, the device including a body containing or coated with a drug selected from the group consisting of at least one bisphosphonate.

- 30 Typically, the drug is free to move from within or on the body of the device to a position outside the body of the device.

 The bone fixation device may be a screw or a number of screws with or without a plate member.

- Typically, the bone fixation device is made from a material including, but
35 not limited to, stainless steel, a titanium alloy or any other biocompatible metal. Alternatively, the fixation device may be made from a bioresorbable material

such as polyglycolide (PGA), poly-(L-lactide), poly (D,L-lactide) (PLA) or another biocompatible polymer. In the latter embodiment, the bisphosphonate may be admixed with the material of the fixation device and delivered to the bone as the fixation device is resorbed thereby releasing the bisphosphonate.

- 5 In another embodiment, a metal device is coated with a layer of bioresorbable material containing a bisphosphonate.

Whether used separately or together with a plate, the screw or screws may contain a therapeutically effective amount of a bisphosphonate. The external surface of the screws may be coated with the at least one
10 bisphosphonate or, alternatively, each screw may include a receptacle member such as a hollow interior, compartment or groove or grooves to house the at least one bisphosphonate.

Where the screw(s) include a receptacle member, the screw(s) may further include an opening or other such structure such as a series of apertures
15 which extend from the receptacle member to an outer surface of the screw(s) such that the at least one bisphosphonate may be released from within the screw to the surrounding bone. In this regard, the opening may be sealed with a resorbable material that breaks down upon placement of the device in a patient's body.

20 In another embodiment where the device is coated with the at least one bisphosphonate, the entire body of the device may be sealed with a resorbable material that breaks down upon placement of the device in a patient's body.

In another embodiment, the plate of the fixation device contains the at least one bisphosphonate. The plate may also be coated with the
25 bisphosphonate or include some other structure to hold the bisphosphonate prior to its release into the fractured bone.

In a further embodiment, the bone fixation device of the invention comprises an intramedullary device. An example of such a device includes, but is not limited to, an intramedullary nail.

30 The fixation device may further comprise an external fixation pin or wire, useful in fractures, osteotomies or arthrodeses managed with external fixation devices. The external fixation pin or wire may also promote bone formation in distraction osteogenesis by providing regional delivery of a bisphosphonate to the bone undergoing distraction.

In another embodiment, the fixation device includes threaded or smooth Kirshner wires wherein the bisphosphonate is deposited on the surface of the wire, or in grooves or hollows of the wires.

In a preferred embodiment of the invention, the at least one
5 bisphosphonate is zoledronic acid {1-hydroxy-2-[(1H-imidazol-1-yl)ethylidene] bisphosphonic acid}.

Alternatively, the at least one bisphosphonate may include, but is not limited to, any one of the following:

- pamidronate {3-amino-1-hydroxypropylidene bisphosphonic acid};
- 10 alendronate {4-amino-1-hydroxybutylidene bisphosphonic acid};
- etidronate {1-hydroxyethylidene bisphosphonic acid};
- clodronate {dichloromethylene bisphosphonic acid};
- risedronate {2-(3-pyridinyl)-1-hydroxyethylidene bisphosphonic acid};
- tiludronate {chloro-4-phenylthiomethylidene bisphosphonic acid};
- 15 ibandronate {1-hydroxy-3(methylpentylamino)-propylidene bisphosphonic acid};
- incadronate {cycloheptyl-amino-methylene bisphosphonic acid};
- minodronate {[1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethylidene]bisphosphonic acid};
- 20 olpadronate {(3-dimethylamino-1-hydroxypropylidene) bisphosphonic acid};
- neridronate (6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid);
- EB-1053 1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid;
- 25 or any other therapeutically effective bisphosphonate or pharmaceutically acceptable salts or esters thereof.

Preferably, the at least one bisphosphonate is administered in the following doses:

- zoledronate at 0.0001 to 0.5 mg/kg body weight per dose;
- 30 pamidronate at 0.0001 to 5.0 mg/kg body weight per dose;
- ibandronate (ibandronic acid) at 0.0001 to 0.5 mg/kg body weight per dose;
- risedronate at 0.0001 to 0.5 mg/kg body weight per dose;
- alendronate at 0.0001 to 5.0 mg/kg body weight per dose;
- 35 clodronate at 0.0001 to 20 mg/kg body weight per dose;
- etidronate at 0.0001 to 20 mg/kg body weight per dose;

tiludronate at 0.0001 to 5.0 mg/kg body weight per dose;
incadronate at 0.0001 to 5.0 mg/kg body weight per dose;
minodronate at 0.0001 to 0.5 mg/kg body weight per dose;
olpadronate at 0.0001 to 0.5 mg/kg body weight per dose;
5 neridronate at 0.01 to 5.0 mg/kg body weight per dose;
EB-153 at from 0.0001 to 5.0 mg/kg body weight per dose.

The at least one bisphosphonate may be admixed with other substances or carriers such as gelatin, glycerol, collagen, hyaluonan-based sponges, pads, pastes and gels, chitosan, fibrin, synthetic polymers, calcium sulphate,
10 tricalcium phosphate, hydroxyapatite or other ceramics, and or their combinations to alter the rate at which the bisphosphonate dose is administered to the fractured bone.

The bone fixation device of the present invention may be used to promote union of a fractured bone.

15 The bone fixation device may also be used to promote the fusion of a joint during an arthrodesis procedure, including spinal arthrodesis (spinal fusion).

In another embodiment, the bone fixation device may be used to promote the union of a bone following an osteotomy procedure.

20 The device may also be used to promote union in a fracture healing slowly (delayed union) or where healing has appreciably ceased (non-union).

The bone fixation device may be used to treat a patient suffering from osteonecrosis or osteochondritis dissecans. Furthermore, the device may be used to treat a patient in need of internal fixation because of osteoporosis and
25 the resultant risk of fracture. Alternatively, the patient may be at risk of pathological fracture.

In another embodiment, the bone fixation device may be used to treat a patient having a pathological fracture secondary to malignant disease. In this embodiment, the at least one bisphosphonate contained within or coated on the
30 device would have the advantage of stimulating fracture repair in addition to preventing further resorption due to the malignant process.

The bone fixation device may further be used to treat a patient suffering from Paget's disease, fibrous dysplasia, osteofibrous dysplasia, congenital pseudarthrosis, osteogenesis imperfecta or other conditions requiring fixation of
35 a fracture.

In another embodiment, the bone fixation device may be used prophylactically in a patient who is receiving or has received systemic corticosteroid or other therapy, is an active smoker, intakes large quantities of alcohol or any other substance known to cause osteoporosis and resultant fracture and to interfere with fracture union.

In the embodiment wherein the bone fixation device comprises a plate member and a plurality of screws, said device may be particularly useful in the promotion of union of fractures of the femur, tibia, fibula, calcaneus, metatarsals, humerus, radius, ulna, metacarpals, maxilla, mandible and cranium, but could be used in any bone where plate fixation is feasible.

When used alone, the screws may be used to treat a patient suffering from a fracture of a small bone such as the scaphoid, talus and femoral neck. This embodiment may also be useful for the treatment of fractures of the spine, fractures involving articular surfaces and fractures around the foot and ankle or hand and wrist. The bone fixation device of this embodiment may also be used in the treatment of osteochondritis dissecans.

In one embodiment, the bone fixation device may be used in the treatment of a patient requiring a spinal or other joint arthrodesis. In this embodiment, the bone fixation device may be used to secure the arthrodesis in such a manner as to potentiate the bony healing necessary to accomplish an effective arthrodesis.

In a further embodiment, the bone fixation device may be used in the treatment of a patient requiring an osteotomy. In this embodiment, the fixation device may be used to secure the osteotomy in such a manner as to potentiate bony healing of the osteotomy.

The bone fixation device of the present invention may be used in humans or alternately in the field of veterinary medicine.

In a second aspect, the invention consists in a method of promoting union of a fracture in a patient in need of such treatment using the device according to the first aspect of the invention, the method including the steps of:

- (a) carrying out reduction of the fractured bone;
- (b) positioning the fixation device such that it fixes the fractured bone in a desired position;
- (c) causing or allowing the delivery of the at least one bisphosphonate from the fixation device to a region of the fractured bone.

The entire dose of bisphosphonate is preferably delivered to a region of bone within the proximity of a fracture site such that the bisphosphonate has the desired effect of promoting bone growth between, and ultimately union of, the fractured ends of the bone. Accordingly, the bone fixation device may be positioned substantially adjacent or across the fracture site or substantially spaced from the fracture site. Furthermore, the bone fixation device may be positioned external the fractured bone or internal the bone.

Preferably, the at least one bisphosphonate is delivered to a sufficient region of bone around the fracture site by diffusion of the drug such that total osteoblastic production of bone is increased in addition to preventing against osteoporosis in the region around the fracture which may result from disuse or from stress shielding by the bone fixation device.

The entire dose of bisphosphonate may be delivered early in the course of healing of the fracture, that is, in approximately the first two weeks following the surgical procedure. The entire dose may, however, be delivered in a more prolonged manner in the course of healing of the fracture for example over approximately the first two months. Alternatively, the entire dose may be delivered over approximately one or more years following the fracture.

In a third aspect, the invention consists in a method of promoting union of an arthrodesis, including a spinal arthrodesis in a patient in need of such treatment using the device according to the first aspect of the invention, the method including the steps of:

- (a) preparing the bone site for arthrodesis by exposing bone surfaces;
- (b) positioning the fixation device such that it fixes the bone or bones in a desired position;

(c) causing or allowing the delivery of the at least one bisphosphonate from the fixation device to a region of the arthrodesis.

In a fourth aspect, the invention consists in a method of promoting union of an osteotomy in a patient in need of such treatment using the device according to the first aspect of the invention, the method including the steps of:

- (a) carrying out reduction of the osteotomised bone;
- (b) positioning the fixation device such that it fixes the osteotomised bone in a desired position;
- (c) causing or allowing the delivery of the at least one bisphosphonate from the fixation device to a region of the osteotomy.

In a fifth aspect, the invention consists in a method of promoting healing of osteochondritis dissecans in a patient in need of such treatment using the device according to the first aspect of the invention, the method including the steps of:

- 5 (a) carrying out reduction of the osteochondritic fragment;
- (b) positioning the fixation device such that it fixes the osteochondritic fragment in a desired position;
- (c) causing or allowing the delivery of the at least one bisphosphonate from the fixation device to a region of the osteochondritic fragment.

10 In a sixth aspect, the invention consists in a method of promoting healing of osteonecrosis in a patient in need of such treatment using the device according to the first aspect of the invention, the method including the steps of:

- (a) drilling a hole in the region of the osteonecrosis;
- (b) positioning the fixation device such that it supports the bone in the
15 region;
- (c) causing or allowing the delivery of the at least one bisphosphonate from the fixation device to a region of the osteonecrosis.

As bisphosphonates have a strong affinity for bone mineral, when the at least one bisphosphonate is delivered to a region of bone surrounding a
20 fracture, arthrodesis site, osteotomy site, site of osteochondritis dissecans or site of osteonecrosis, the bisphosphonate should be taken up locally in that region of bone thus minimising the distribution of the bisphosphonate to other regions of the body (ie systemic distribution).

The fixation device of the present invention does not include an
25 orthopaedic prosthesis such as a prosthetic joint or dental replacement device wherein the provision of bisphosphonates would enhance securement of the prosthetic device in the surrounding bone.

Brief Description of the Drawings

30

By way of example only, a preferred embodiment of the invention is described with reference to the accompanying figures:

Fig. 1 is a generic formula for one class of bisphosphonates.

Fig. 2 is a schematic view of one embodiment of the present invention.

35 Fig. 3 is a schematic view of a further embodiment of the present invention.

Fig. 4 is a schematic view of another embodiment of the present invention.

Preferred Embodiment of the Invention

5

The invention relates to the use of a bisphosphonate with the general formula depicted in Figure 1 wherein R_1 is varied to give binding and solubility properties to the bisphosphonate and R_2 is varied to give various potencies and other properties to the bisphosphonate.

10 An orthopaedic fixation device according to the present invention is generally depicted in the accompanying drawings as 10.

The fixation device 10 includes a central canal 11 which receives a therapeutic dose of bisphosphonate. The side vent holes 12 allow the bisphosphonate to diffuse out of the fixation device 10 and be taken up by the
15 bone in the region of the fixation device 10. The fixation device is preferably positioned sufficiently close to a fracture site to allow for diffusion of the bisphosphonate to said fracture site. Such local or regional administration and binding of the bisphosphonate leads to the prevention of the unwanted bisphosphonate dosing of other areas of the body.

20 The device depicted in Figure 3 is positioned within a fractured scaphoid bone 13. The fixation device 10 comprises a screw 20 which may be countersunk under the articular surface 14. The screw 20 provides compression of the fractured bone. The screw 20 further includes a groove 15 which is adapted to receive and hold a therapeutically effective dose of
25 bisphosphonate. Alternatively, an external surface of screw 20 may be coated with the therapeutically effective amount of bisphosphonate. Scaphoid fractures are known to have a high incidence of delayed union and osteonecrosis. Both these conditions may be ameliorated by the local administration of a bisphosphonate.

30 As depicted in Figure 4, the fixation device 10 may include a plate 30 having a series of screws 20 dependent therefrom. The screws 20 are drilled into the bone such that both the plate 30 and the screws 20 fix the bone in place. As previously discussed, either the plate 30 or the screws 20 may be contain a therapeutic amount of bisphosphonate. Further, both the plate 30
35 and the screws 20 may contain a therapeutic amount of bisphosphonate.

Example 1

Animal Model

- 5 The present experiment uses 20 to 24 -week-old NZW rabbit model. Animals were approximately 3 kg at the time of surgery. A 10mm segmental fracture is surgically created in the right tibiae of the rabbits. The bones are held with a 7 hole plate and screws.

10 **Experimental Groups**

16 animals were allocated into one of four groups (4 per group)

- i) Saline (Control)
- ii) 1mg pamidronate, delivered via plate (1mg plate)
- 15 iii) 8mg pamidronate, delivered via plate (8mg plate)
- iv) 5mg pamidronate, delivered via cannulated screw (5mg screw)

Device Preparation

- 20 All plates were identical in design, ¼ tubular plates with 7 holes and 55 mm in length, made to fit 2.7mm screws, but also compatible with 3.5 mm screws. Plates were prepared by autoclave sterilisation. For 1mg plates, a solution of pamidronate 10 mg/ml was prepared and 0.1 ml (1mg) was distributed on the concave side of the plate. This is the side in direct contact with
- 25 bone. For 8 mg plate, a solution of pamidronate 25 mg/ml was prepared and 0.3 ml (approx 8mg) was applied to the concave side of the plate. Plates were placed in sterile Petrie dishes and incubated for 12 hrs at 37° C until dry, prior to implantation.

- Delivery screws were of a special design. A 3.5 mm cortical bone screw
- 30 had been cannulated with a 1.1 mm hole and a 0.7 mm side vent hole (Fig 1). 5mg of pamidronate was placed in the sterile screw immediately prior to surgery.

Operative Technique

- 35 Surgery was performed in an animal theatre. After premedication with IM ketamine 15 mg/kg, xylazine 4mg/kg given in combination 10 minutes before

surgery, anaesthesia was maintained with inhaled halothane 2%, nitrous oxide 2 litres/min and oxygen 1L/min.

The operative field was prepared by shaving with clippers, disinfected with povidone iodine 4% w/v in 70% alcohol. The tibia was exposed sub-periosteally along its length and a spare plate used as a template to allow pre-drilling and tapping of fixation holes. Drill sites were placed in holes 1, 2, 4, 6 and 7 (proximal to distal) – holes 3 and 5 were not used as they were close to the planned osteotomies. Two osteotomies were created with a saw and a 10 mm piece of mid-diaphyseal tibia removed and replaced. The designated 7-hole ¼ tubular plate was then attached to the tibia, 2 screws in each large segment and one screw in the de-vascularised central segment. All screws were 2.7mm cortical screws apart from the screw in the second hole, which was 3.5mm. In the 5mg screw group, the cannulated screw contained disodium pamidronate powder.

Wounds were closed with dissolvable suture and Buprenorphine 0.05 mg/kg was given at the end of surgery and 12 hours post-operatively. Animals were allowed to freely weight bear.

Exclusions

One rabbit in the screw group was excluded as the central segment had been split at surgery and fixation did not hold.

Analysis

Animals were culled at six weeks post operation. Both tibiae were harvested and the plates and screws removed. The whole bones were fixed in 4% paraformaldehyde. The tibiae were analysed with a Stratec XCT Research SA pQCT scanner and analysis software (Stratec Medizintechnik GmbH, Pforzheim, Germany). Scout scans were centred on the central screw hole and scans taken proximally 20mm, 10mm 5 mm and 2.5 mm from the centre, through the centre and 2.5 mm, 5 mm, 10mm and 20mm distally on the right (operated) leg. On the left (non-operated) leg, scans were taken in corresponding areas at the centre, and 10mm proximal and distal.

The scanner generated data for BMD, BMC, cross sectional area and polar moment of inertia. The callus volume was integrated from mean cross

sectional area and scan length. With $n=3-4$ data points, quantification of parametric statistical differences is limited, and was not used. Chi square analysis was applied to compare numbers of scan regions showing differences of greater than 10%.

5

Results

Total bone volume is shown in Graph 1. Bone volume on the operated side was increased by 26% in the 5mg screw group. There were only slight differences in the plate groups.

Cross-sectional area for all regions in all groups is presented in Graph 2. There were increases in cross sectional area in the screw group over controls on the operated side ranging from 13% to 38% (median 27%), but no increase on the non-operated leg. The median increases in the 1mg and 8mg plate groups were 5% and 5%, respectively. The differences were greater than 10% in 9 of 9 scan regions for the screw group, in contrast in only 2 of 9 regions was there an increase of $>10\%$ in area in the 1mg plate group, and in only 4 of 9 regions was this the case in the 8mg plate group. This was significant by chi square $p<0.01$.

Bone mineral content was likewise increased in the screw group (Graph 3). For clarity, remaining graphs show only the control and screw groups. The increases in the different scan regions ranged from 9% to 22% (median 16%). There was no increase in the non-operated leg. The median increases in the 1mg and 8mg plate groups were 6% and 6%, respectively. The differences were greater than 10% in 8 of 9 scan regions in the screw group, in contrast, in only 2 of 9 regions was there an increase of $>10\%$ in BMC in the 1mg plate group, and in only 3 of 9 regions was this the case in the 8mg plate group. This was significant by chi square $p<0.025$.

Polar moment of inertia was increased in the 5mg screw group by 49% to 87% (median 71%) over controls. There was no increase in the non-operated leg. In contrast the 1mg plate and 5 mg plate showed little or no improvement in polar moment (median 0% and -8% , respectively). All 9 areas showed increases of over 40% in the 5mg screw group, whereas only 1 of 9 and 0 of 9 showed this level of increase in the 1mg and 8mg plate groups ($P<0.01$ chi square).

There was no notable difference in volumetric BMD between any of the operated groups.

Discussion

5

This experiment looks at the effect of regional bisphosphonate dosing via a delivery device for fracture care. The inventor has previously documented that systemic bisphosphonate delivery can increase the amount, mineral content and strength of callus during bone healing. In a systemic pamidronate
10 study, increases in BMC were noted on the operative side, but also increases in BMC of 10%-12% were seen on the non-operative side.

The advantages of regional delivery are numerous, including: increased amount, mineral content and strength of callus; reduced bone exposure away from the target region; and reduced renal exposure and therefore reduced risk
15 of nephrotoxicity.

The results of the experiment show that bisphosphonates may be successfully delivered to the region of a fracture. Dosing on the plate itself did not lead to a notable improvement in the parameters measured. In this regard, it is possible that the pamidronate was "trapped" between the plate and the
20 bone and was only delivered to the area immediately beneath the plate. It is notable that one of the plate groups received a higher dose than the screw group, with lesser effect on outcome.

In contrast the dosing screw allowed the pamidronate to diffuse into the region of the fracture haematoma, and its effects can be seen to have occurred
25 at both the proximal and distal osteotomy sites (Graphs 3-5). This indicates that the dosing was regional and not directly local. There was no change in BMC on the non-operated side in the 5mg screw group. This indicates that only very small amounts of bisphosphonate are likely to have travelled systemically to the other limb. We have noted increases of around 10% in
30 BMC on the non-operated side in both a previous systemic pamidronate and zoledronic acid experiment.

The increases in moment of inertia in the screw group were large (49% to 87%) which is likely to correlate with increases in strength.

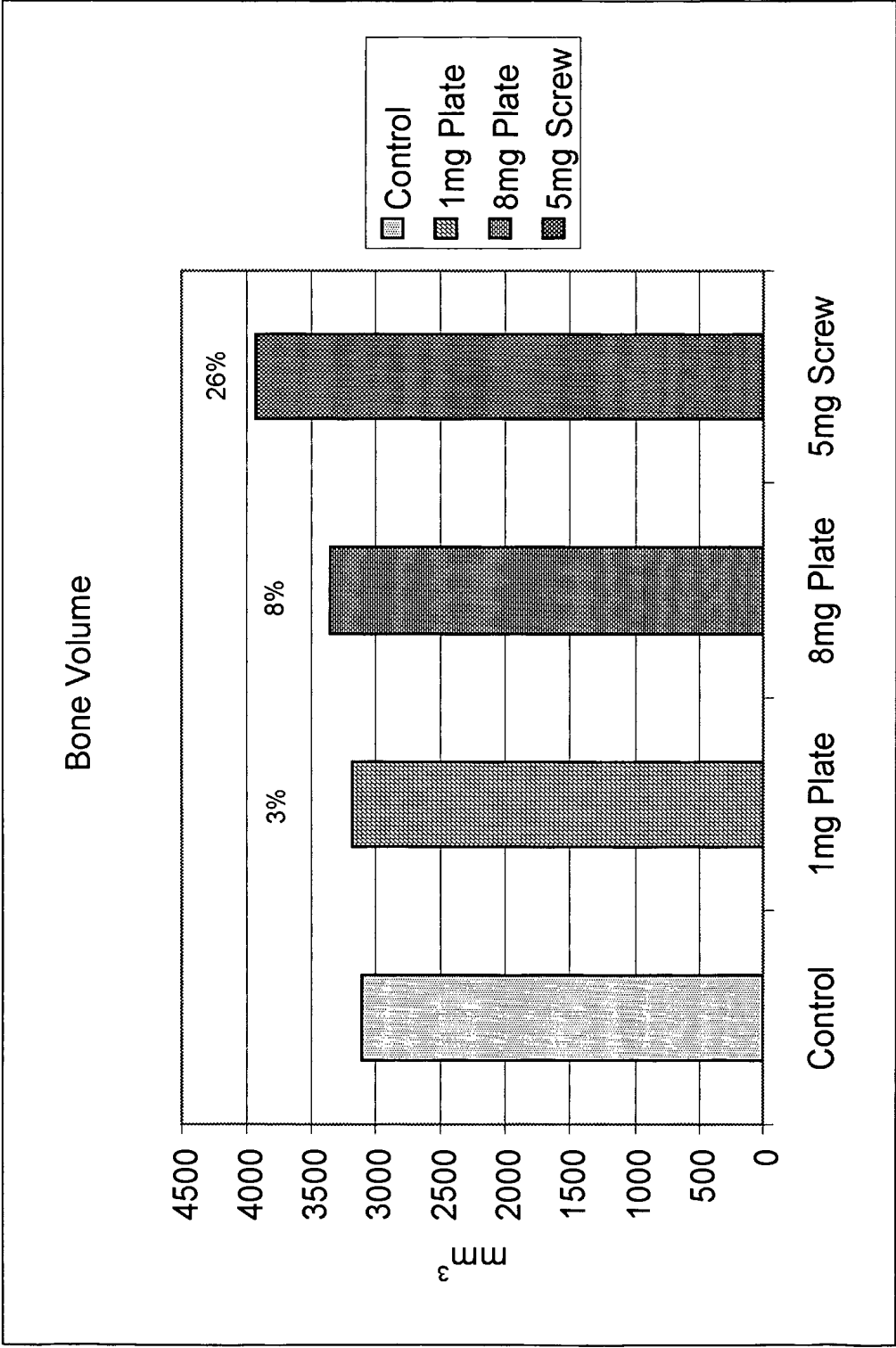
This technique allows the regional treatment of fractures where there is
35 concern about union or stress-shielding osteopenia while minimising systemic exposure.

Conclusions

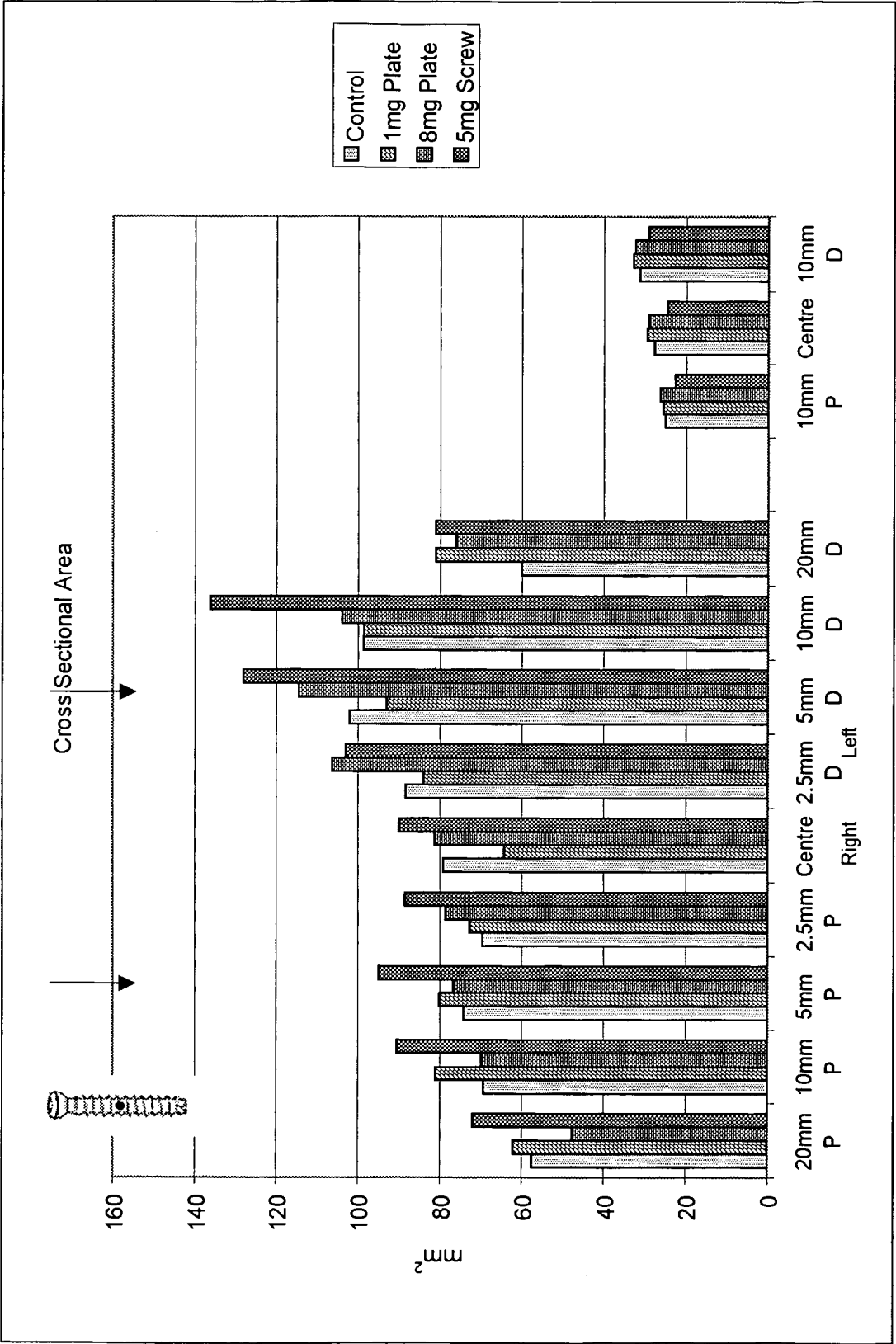
5 This experiment indicates that regional delivery of pamidronate via an internal fixation device, a cannulated screw in this case, can result in increases in area, mineralisation and moment of inertia in a double osteotomy model in NZW rabbits. No effect was seen in the contralateral limb, in contrast to previous systemic dosing experiments. Delivery of pamidronate via the plates was ineffective; it is possible the drug was sequestered under the plate.

10 It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

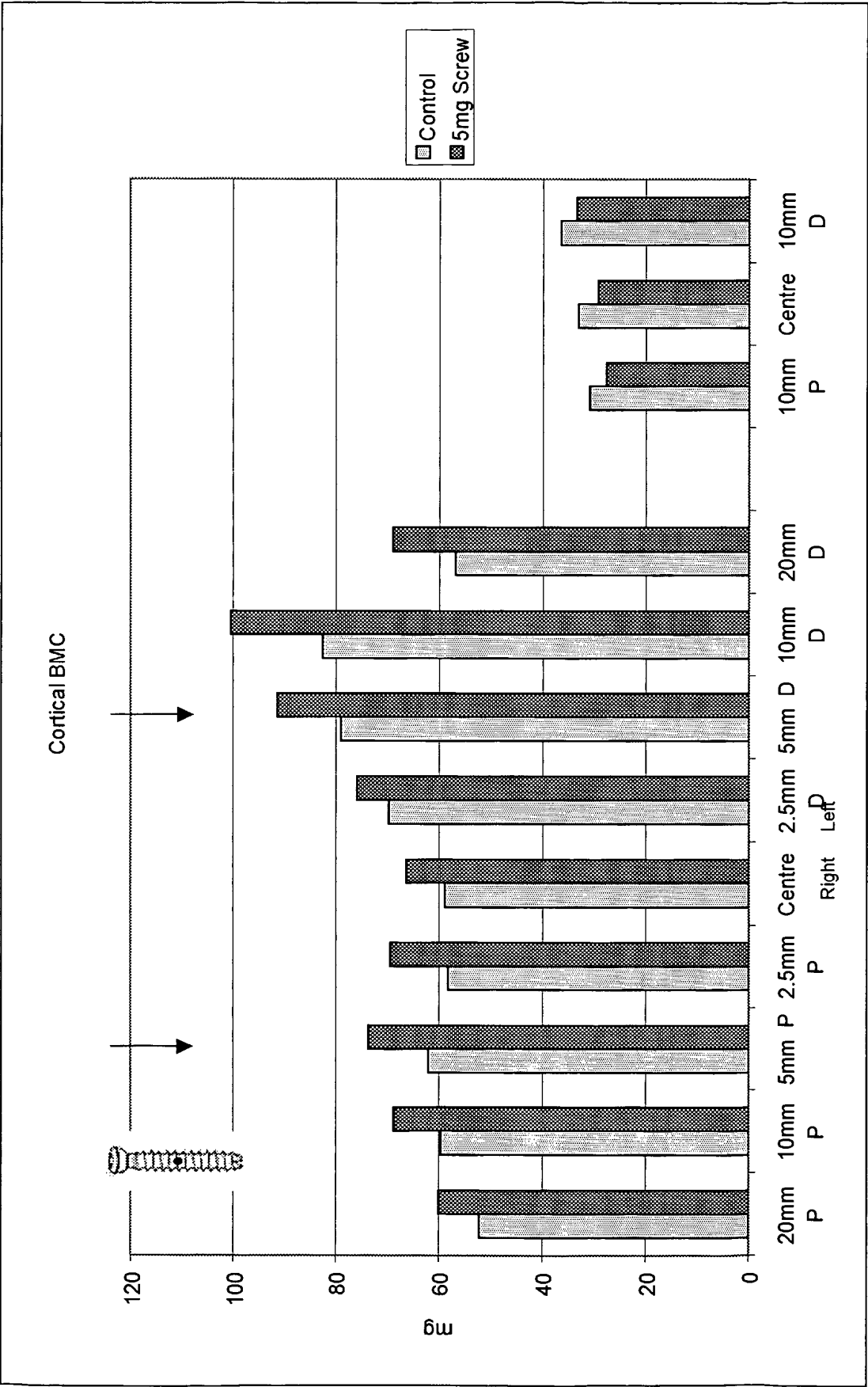
Graph 1 Bone Volume



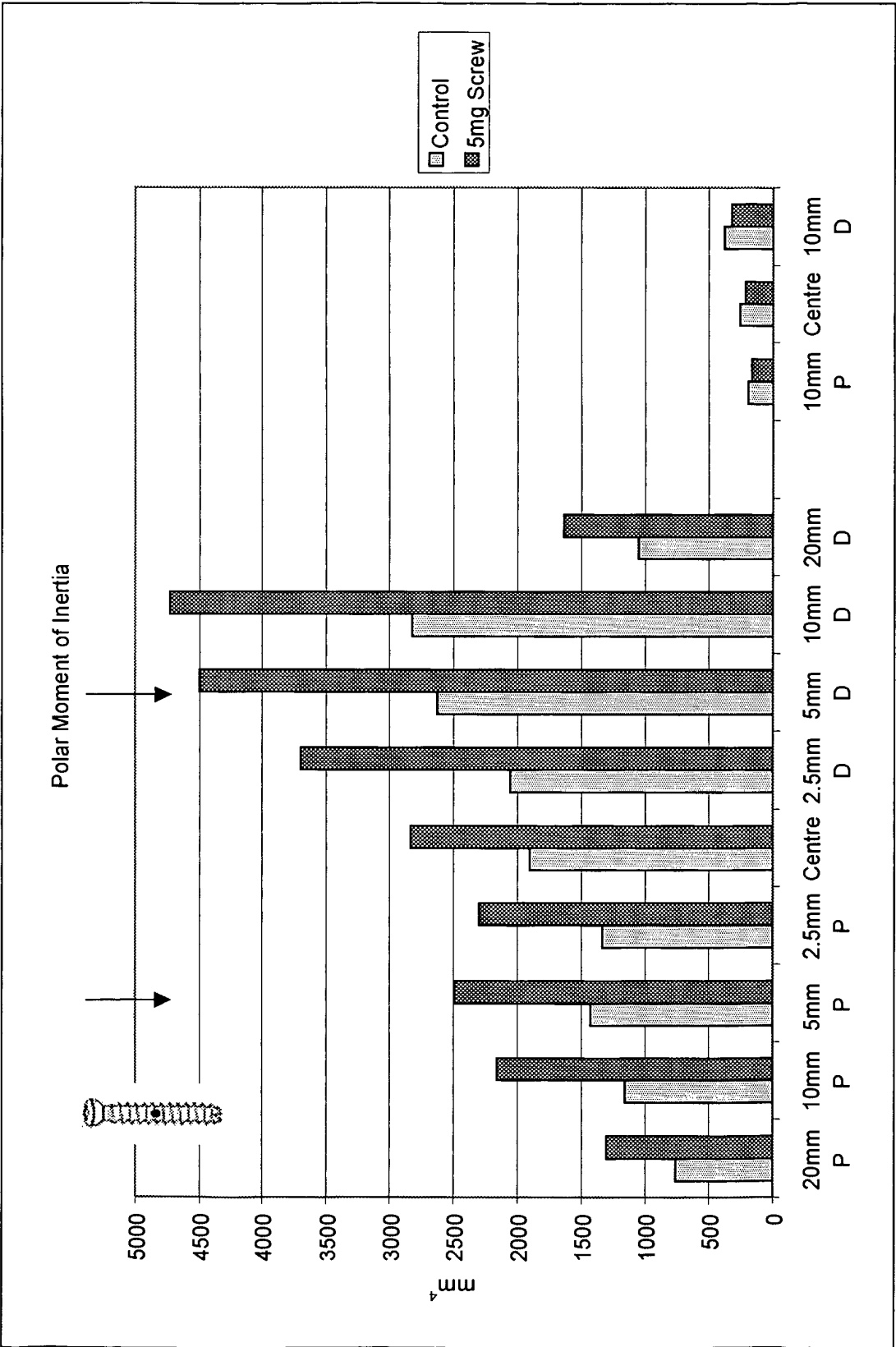
Graph 2 Cross-Sectional Area (Screw denoted position of dosing screw, arrows denote sites of osteotomies)



Graph 3 BMC in Control and 5mg screw dosing groups (Screw denoted position of dosing screw, arrows denote sites of osteotomies)



Graph 4 Polar moment of inertia in Control and 5mg screw dosing groups (Screw denoted position of dosing screw, arrows denote sites of osteotomies)



CLAIMS:

1. A bone fixation device, the device including a body containing or coated with a drug selected from the group consisting of at least one bisphosphonate.
2. The bone fixation device of claim 1 wherein said device comprises at
5 least one screw.
3. The bone fixation device of claim 2 wherein the at least one screw includes a receptacle member to receive the at least one bisphosphonate.
4. The bone fixation device of claim 3 wherein the receptacle member comprises a hollow interior, compartment or groove and wherein the device
10 further includes an aperture or a series of apertures extending from the hollow interior, compartment or groove to an external surface of the screw.
5. The bone fixation device of claim 4 wherein the aperture or series of apertures are sealed with a material that is resorbable within a body of a subject.
- 15 6. The bone fixation device of claim 2 wherein the external surface of the at least one screw is coated with the at least one bisphosphonate.
7. The bone fixation device of any one of claims 2 to 6 further including a plate member having an aperture or a series of apertures therein to receive the at least one screw.
- 20 8. The bone fixation device of claim 7 wherein the plate member is coated with the at least one bisphosphonate.
9. The bone fixation device of any one of the preceding claims wherein said device is made from a material selected from the group comprising stainless steel, a titanium alloy or any other biocompatible metal.
- 25 10. The bone fixation device of any one of claims 1 to 8 wherein said device is made from a bioresorbable material including polyglycolide (PGA), poly-(L-lactide), poly-(D,L-lactide) (PLA).
11. The bone fixation device of claim 10 wherein the at least one bisphosphonate is admixed with the material of the bone fixation device.
- 30 12. The bone fixation device of claim 1 wherein said device comprises an intramedullary device including an intramedullary nail.
13. The bone fixation device of claim 1 wherein said device comprises an external fixation pin or wire.
14. The bone fixation device of claim 1, said device comprising threaded or
35 smooth Kirshner wires wherein the at least bisphosphonate is deposited on the surface of the wire, or in grooves or hollows of the wires.

15. The bone fixation device of any one of the preceding claims wherein the at least one bisphosphonate is zoledronic acid {1-hydroxy-2-[(1H-imidazol-1-yl)ethylidene] bisphosphonic acid}.
16. The bone fixation device of any one of claims 1 to 14 wherein the at least
5 one bisphosphonate is selected from the group consisting of pamidronate {3-amino-1-hydroxypropylidene bisphosphonic acid}; alendronate {4-amino-1-hydroxybutylidene bisphosphonic acid}; etidronate {1-hydroxyethylidene bisphosphonic acid}; clodronate {dichloromethylene bisphosphonic acid}; risedronate {2-(3-pyridinyl)-1-hydroxyethylidene bisphosphonic acid};
10 tiludronate {chloro-4-phenylthiomethylidene bisphosphonic acid}; ibandronate {1-hydroxy-3(methylpentylamino)-propylidene bisphosphonic acid}; incadronate {cycloheptyl-amino-methylene bisphosphonic acid}; minodronate {[1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethylidene]bisphosphonic acid}; olpadronate {(3-dimethylamino-1-hydroxypropylidene) bisphosphonic acid}; neridronate (6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid); EB-1053 1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid; or any other therapeutically effective bisphosphonate or pharmaceutically acceptable salts or esters thereof.
17. The bone fixation device of any one of the preceding claims wherein the
20 at least one bisphosphonate is admixed with a carrier medium including gelatin, glycerol, collagen, hyaluronan-based sponges, pads, pastes and gels, chitosan, fibrin, bioresorbable polymers, silicon, calcium sulphate, tricalcium phosphate, hydroxyapatite or other ceramics, or any drug delivery system.
18. The bone fixation device of any one of the preceding claims when used
25 to promote union of a fractured bone including the promotion of union in delayed or non-union fractures.
19. The bone fixation device of any one of claims 1 to 17 when used to promote the fusion of a joint during an arthrodesis procedure, including spinal arthrodesis (spinal fusion).
- 30 20. The bone fixation device of any one of claims 1 to 17 when used to promote the union of a bone following an osteotomy procedure.
21. The bone fixation device of any one of claims 1 to 17 when used in the treatment of osteonecrosis or osteochondritis dissecans.
22. The bone fixation device of any one of claims 1 to 17 when used to treat
35 a patient in need of internal fixation due to osteoporosis and the associated risk or fracture.

23. The bone fixation device of any one of claims 1 to 17 when used to treat a patient having a pathological fracture secondary to malignant disease.

24. A method of promoting union of a fracture in a patient in need of such treatment using the bone device of claim 1, the method including the steps of:

- 5 (a) carrying out reduction of the fractured bone;
- (b) positioning the bone fixation device such that it fixes the fractured bone in a desired position;
- (c) causing or allowing the delivery of a dose of the at least one bisphosphonate from the bone fixation device to a region of the fractured bone.

10 25. The method of claim 24 wherein the bone fixation device is positioned substantially adjacent or substantially spaced from the fracture site.

26. The method of claim 24 or claim 25 wherein the entire dose of the at least one bisphosphonate is delivered to a region of bone within the proximity of the fracture site within the first two weeks following the surgical procedure.

15 27. The method claim 24 or claim 25 wherein the entire dose is delivered to a region of bone within the proximity of the fracture site over a period of two months following the surgical procedure.

28. The method of claim 24 or claim 25 wherein the entire dose is delivered to a region of bone within the proximity of the fracture site over a period of one
20 or more years following the surgical procedure.

29. A method of promoting union of an arthrodesis, including a spinal arthrodesis in a patient in need of such treatment using the bone fixation device of claim 1, the method including the steps of:

- (a) preparing the bone site for arthrodesis by exposing bone surfaces;
- 25 (b) positioning the bone fixation device such that it fixes the bone or bones in a desired position;
- (c) causing or allowing the delivery of the at least one bisphosphonate from the bone fixation device to a region of the arthrodesis.

30 30. A method of promoting union of an osteotomy in a patient in need of such treatment using the bone fixation device of claim 1, the method including the steps of:

- (a) carrying out reduction of the osteotomised bone;
- (b) positioning the bone fixation device such that it fixes the osteotomised bone in a desired position;
- 35 (c) causing or allowing the delivery of the at least one bisphosphonate from the bone fixation device to a region of the osteotomy.

31. A method of promoting healing of osteochondritis dissecans in a patient in need of such treatment using the bone fixation device of claim 1, the method including the steps of:

- (a) carrying out reduction of the osteochondritic fragment;
- 5 (b) positioning the bone fixation device such that it fixes the osteochondritic fragment in a desired position;
- (c) causing or allowing the delivery of the at least one bisphosphonate from the bone fixation device to a region of the osteochondritic fragment.

32. A method of promoting healing of osteonecrosis in a patient in need of
10 such treatment using the bone fixation device of claim 1, the method including the steps of:

- (a) drilling a hole in the region of the osteonecrosis;
- (b) positioning the fixation device such that it supports the bone in the region;
- 15 (c) causing or allowing the delivery of the at least one bisphosphonate from the bone fixation device to a region of the osteonecrosis.

Fig. 1

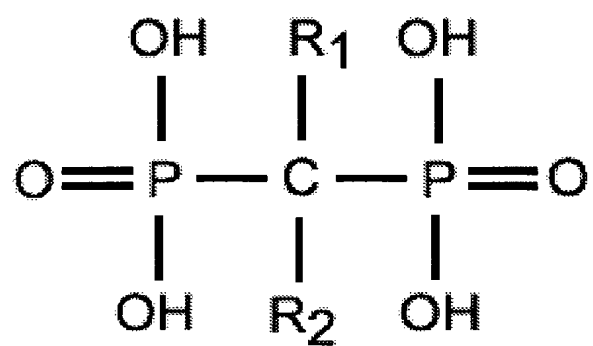


Figure 2

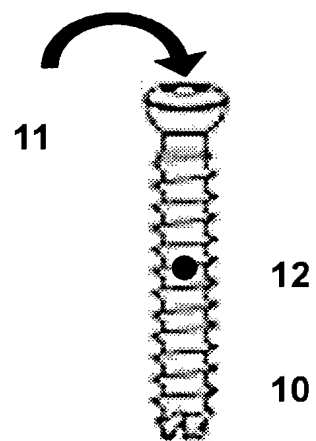
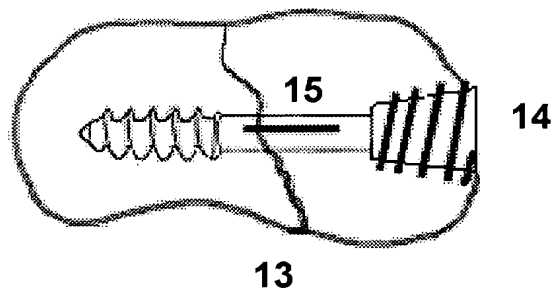


Figure 3



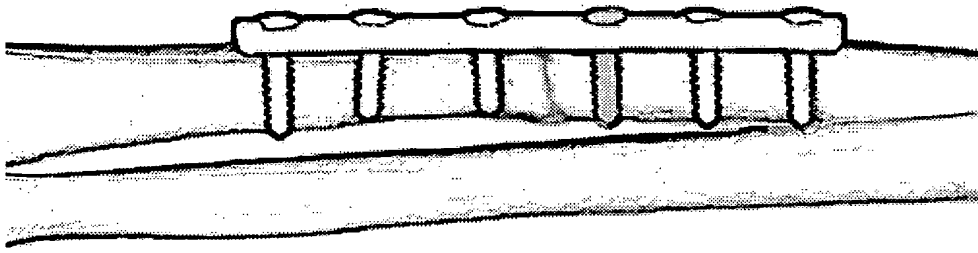
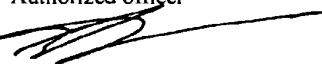


Figure 4

INTERNATIONAL SEARCH REPORT

 International application No.
PCT/AU02/00482

A. CLASSIFICATION OF SUBJECT MATTER					
Int. Cl. ⁷ : A61B 17/86; A61K 031/663; A61P 19/00					
According to International Patent Classification (IPC) or to both national classification and IPC					
B. FIELDS SEARCHED					
Minimum documentation searched (classification system followed by classification symbols)					
IPC: A61K, SEARCH TERMS AS BELOW					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched					
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)					
WPAT, CAPLUS, MEDLINE: (bone OR osteotom: OR arthrodes:) AND (screw OR plate OR device OR prosthesis OR implant) AND (bisphosphonate OR diphosphonate OR biphosphonate OR zolendron: OR palmidron: OR alendron: OR clodron: OR risedron:)					
C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.			
X	WO 00/00177A (ISIS Innovation Limited) 6 January 00 See whole document	1-2, 6-10, 12-32			
X	WO 01/13922A (The Royal Alexandra Hospital for Children) 1 March 2001 See whole document	1-2, 6-10, 12-32			
X	WO 94/14455A (Merck & Co., Inc.) 7 July 1994 See whole document	1-2, 6-10, 12-32			
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex					
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%; vertical-align: top;"> * Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td style="width: 33%; vertical-align: top;"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family </td> <td style="width: 33%;"></td> </tr> </table>			* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family	
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family				
Date of the actual completion of the international search 4 June 2002	Date of mailing of the international search report 20 JUN 2002				
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No. (02) 6285 3929	Authorized officer  MICHAEL GRIEVE Telephone No : (02) 6283 2267				

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU02/00482

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/28936A (Merck & Co., Inc.) 2 November 1995 See whole document	1-2, 6-10, 12-32
X	Denisson, H. et al. "Degradable Bisphosphonate-Alkaline Phosphatase-Complexed Hydroxyapatite Implants In Vitro" Journal of Bone and Mineral Research Vol.12(2) (1997) pages 290 to 297 See whole document	1-2, 6-8, 10, 12-32
X	Denisson, H. et al. "Ceramic Hydroxyapatite Implants for the Release of Bisphosphonate" Bone and Mineral Vol.25(2) (1994) pages 123-134 See whole document	1-8, 10, 12-32
X	Horowitz, S.M. et al. "Inflammatory Response to Implant Particulates in a Macrophage/Osteoblast Coculture Model" Calcified Tissue International Vol.59(5) (1996) pages 392 to 396 See whole document	1-32
A	WO 00/25809A (Smith & Nephew PLC) 11 May 2000 See whole document	1-32

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU02/00482

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
WO	2000/00177	EP	1089711		
WO	2001/13922	AU	200065488	BR	200013416
WO	94/14455	AU	59538/94	CA	2151240
				EP	675723
WO	95/28936	AU	23748/95	AU	35747/99
		CA	2188030	CN	1146152
		EP	756483	EP	1197213
		HR	950239	HU	74911
		NO	964441	NZ	284295
		SK	1333/96	US	5646134
		US	5891863	US	5972913
WO	2000/25809	AU	200010549		
END OF ANNEX					